Cell Phone Usage and Acoustic Neuroma: The Need for Standardized Questionnaires and Access to Industry Data

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Abbreviation List:

AN = acoustic neuroma
OR = odds ratios
CI = confidence interval
RF = radiofrequency
US = United States
MRI = magnetic resonance image
CT = computed tomography
UK = United Kingdom
IARC = International Agency for Research on Cancer
RR = relative risk
SIR = standardized incidence ratio
ICD-O = International Classification of Disease for Oncology (ICD-O)

ABSTRACT

OBJECTIVE: The capacity of radiofrequency from cell phones to be absorbed into the brain has prompted concerns that regular cell phone use may increase the risk of acoustic neuroma (AN) and other brain tumors. This paper critically evaluates current literature on cell phone use and AN risks and proposes additional studies to clarify any possible linkage.

METHODS: Through a PubMed search, we identified and reviewed ten case-control studies and one cohort study of AN risks associated with cell phone use, and a meta-analysis of long-term mobile phone use and its association with AN and other brain tumors.

RESULTS: Most studies did not find association between the development of AN and cell phone use, but some studies that followed cases for 10 years or more did show an association. Among 10 case-control studies, odds ratios (OR) for AN associated with regular cell phone use ranged from 0.5 (95% confidence interval (CI) = 0.2-1.0) to 4.2 (95% CI = 1.8-10). Cell phone use was not associated with increased risk for AN in the Danish cohort study, which excluded business users from their study. The meta-analysis, which included three case-control studies, found that subjects who used cell phones for at least 10 years had a 2.4-fold greater risk of developing ipsilateral AN. In general, retrospective studies are limited in the ability to assess cell phone exposure because of recall bias and misclassification.

CONCLUSIONS: The evaluation of AN risk factors is challenging due to its long latency. Some studies of longer term cell phone use have found an increased risk of ipsilateral AN. Adopting a prospective approach to acquire data on cell phone use, obtaining retrospective billing records that provide independent evaluations of exposures, and incorporating information on other key potential risk factors from questionnaires could markedly advance the capacity of studies to evaluate the impact of cell phones on AN.

INTRODUCTION

Cell phones were introduced to the general public in the late 1980s and their use has grown exponentially in the past decade (Table 1). Currently, more than 90% of the populations in Western Europe and approximately 90% of the United States (US) population use cell phones. The average age to begin cell phone use has been decreasing. Studies have suggested that radiofrequency (RF) (28) signals may have biological effects on target cells or tissues (7, 14). Worldwide use of cell phones has raised concerns that such technology may increase the risk of malignant brain tumors and of acoustic neuroma (AN) -- a benign tumor arises on the eighth cranial nerve that leads from the brain to the inner ear.

Acoustic neuroma affects approximately 1 out of 100,000 people between the ages of 30 and 60 per year. An increase in detection of AN in recent years has been chiefly attributed to the wide spread availability of magnetic resonance imaging (MRI) and computed tomography (CT) scans, although the possibility of an underlying increase cannot be dismissed. In Denmark, the incidence doubled from 5 cases per million population per year in 1977–1981 to 10 cases in 1992–1995 (15). Age-standardized 3-year moving average incidence rates in the United Kingdom (UK) increased threefold from 2.4 to 7.6 per million between 1980 and 1997 (25). Based on 11 Central Brain Tumor Registries in the United States, the reported AN incidence increased approximately 14% per year between 1992 and 1999 (26). To date, it has not been possible to differentiate a real increase in AN development from better or earlier detection as a result of increased use of diagnostic technology.

Studies published to date cannot adequately determine whether cell phone use or other exogenous environmental factors such as increasing noise may have contributed to the increased rates of AN. In 1997, the International Agency for Research on Cancer (IARC) coordinated an international collaborative case-control study on cell phone use and the incidence of brain tumors in 13 countries (the INTERPHONE study). All of these studies relied on self-reported cell phone use through various questionnaires. The results of these studies remain controversial, in part because most studies suffer from various methodological deficiencies including: insufficient statistical power to detect an excess risk of brain tumors; reliance on small populations; short-term exposure periods; and difficulty in characterizing changing exposures throughout a lifetime in large populations. In addition, most negative studies have been substantially funded by the cell phone industry (16).

This paper critically reviews current epidemiologic studies of AN to clarify their limitations and provide suggestions for future studies to systematically collect informative data on cell phone use and AN risks.

METHODS

We searched PubMed (www.ncbi.nih.gov) for published articles on the association between cell phone use and brain tumors, with an emphasis on AN. Using MeSH terms “acoustic neuroma” and “cell phone” in combinations of reviews, articles highly relevant to the subject field were selected. Additional keywords such as “mobile phone,” “brain tumor,” “glioma” and “meningioma” were also entered in PubMed and Medline to search the database. We identified twelve articles, including one cohort study, ten case-control studies, and one meta-analysis on the risk of AN associated with cell phone use. The authors systematically reviewed all studies, summarized major findings, and analyzed the strength and weakness of the study design. The recommendations were developed to devise standardized approaches for evaluating cell phone use and AN or other brain tumor risk.

RESULTS

We analyzed studies involving benign brain tumors, primarily AN, in order to evaluate the potential health hazard of cell phone use (Table 2 and Table 3). Two case-control studies conducted in the US, where cases used cell phones for less than ten years, reported no association between AN development and cell phone use. One of the studies recruited 96 AN patients in 4 hospitals in the US between 1994 and 1998, a period when less than 10 % of the population used cell phones, obtained a 1.9 relative risk (RR) associated with regular cell phone use for AN (95% CI = 0.6-5.9) (18). However, the small sample size does not provide sufficient power to find a significant RR for AN. A similar result was reported by Muscat and his colleagues (24). The major limitations of the two studies were lack of precision for capturing historical changes of cell phone use, short period of use, and inability to evaluate daily use more typical of contemporary patterns. These limitations can introduce misclassification of exposures and cause false negative results.

A Danish study, Christensen et al., first reported results from the INTERPHONE study. The overall estimated risk of AN in cell phone users did not differ from non-users (OR = 0.9, 95% CI = 0.5-1.6). Use of a cell phone for 10 years or longer did not increase AN risk compared to short-term use. However, selection bias was introduced due to a high rate of loss of cases and a lack of information on the selection process for control groups.

More INTERPHONE studies have reported their research on AN development and cell phone uses by case-control design. Studies conducted in Southern Norway (19) and Germany (28) found no excess AN risk in regular cell phone users (OR = 0.5, 95% CI = 0.2-1.0 and OR = 0.7, 95% CI = 0.4-1.2, respectively). Regardless of laterality, regular cell phone use or use cell phone more than 10 years did not raise the OR of AN in a pooled data set in the UK and four Nordic countries (29) nor in a Swedish study conducted by Lönn et al. (23). In Japan, Takebayashi and his colleagues reported no significant increases of AN risk among regular cell phone users. A cumulative length of more than eight years of cell phone use did not increase the risk (31). The case numbers of heavy users were too small to reach a statistical significance. In general, selection bias was introduced in these studies because of lower response rates among controls and the definition of exposure used. Due to small numbers of long-term users, these studies fall short in their ability to evaluate the long-term effect of cell phone exposure.

A nationwide Danish cohort study conducted by Schüz and his colleagues recruited about 420,000 cell phone users from 1982 to 1995 and found that cell phone use did not increase the risk of AN (Standardized Incidence Ratio, SIR = 0.7, 95% CI = 0.4-1.3) (30). The study used objective exposure measurements that derived from the files of Danish network providers. However, the study excluded those likely to be the greatest users of cell phones—business users ad teenagers. A total of 200,507 business users were excluded from the study. An additional 102,819 users were excluded because of errors in name or address, their age was under 18, or they subscribed to cell phone services after 1995. Elimination of the presumably heavier business users and teenagers has biased results toward the null hypothesis, or false negative findings. In addition, a regular user in this study, and in all INTERPHONE studies, was defined as a person making at least one call a week; a misclassification found in many cell phone studies. Misclassification has caused underestimation of the risk or a false negative finding because the majority of the control population consisted of recent cell phone users. Thus, for both this cohort study and for case-control studies, exposure assessment remains highly problematic due to reliance on the individuals who self-reported and included infrequent users as exposed.

In contrast to these negative findings, Hardell and his colleagues conducted a series of study in Sweden, a country with longer term cell phone use by a greater proportion of the population. They found using cell phone increase the risks of AN and other brain tumors. In 2002, they conducted a study on AN patients aged 20-80, who regularly used a cell phone for one year or more versus those who never or rarely used a cell phone and reported an OR of 3.5 (95% CI = 1.8-6.8) (13). Between 2000 and 2003, they performed a similar study and reported an OR of 4.2 (95% CI = 1.8-10) for analogue phones and 2.0 (95% CI = 1.05-3.8) for digital phones (9). In a recent analysis, the Hardell group combined information from nine case-control studies (824 cases) of AN risk and reported that regular cell phone users had no increased AN risk (OR = 0.9, 95% CI = 0.7-1.1) (11). These studies are limited because of the self-reported nature of cell phone use, recall bias from long-term exposures and misclassification of cell phone exposure.

Laterality of tumor and of handheld cell phone use has been investigated (Table 2). Two US studies and one Danish study did not find an increased relative risk of AN and laterality of regular cell phone use (5, 18, 24). In four case-control studies, including three European studies and one Japanese study, the laterality of the AN was not significantly associated with self-reported laterality of cell phone use (19, 23, 29, 31). In contrast, the Hardell group found a consistent pattern of an association between ipsilateral AN and cell phone use in the context of a 10-years latency period or longer. Results from the meta-analysis indicated that those who used cell phones for at least 10 years had a 2.4-fold (95% CI = 1.1-5.3) greater risk of developing ipsilateral AN (11). The conclusion was supported by two additional studies from the Nordic region. Lönn et al. reported a significant increased AN associated with ipsilateral cell phone use of at least 10-year duration (OR = 3.9, 95% CI = 1.6-9.5) (23). Schoemaker et al. also found an increased AN for ipsilateral cell phone users for 10 years or more (OR = 1.8, 95% CI = 1.1-3.1)(29). Hearing loss associated with AN may have influenced the current findings. Apart from recall bias, the results may be distorted toward null because of lower participation rates among cases due to hearing impairment and death, or because AN patients were more likely to have used the cell phone on the contralateral ear due to hearing impairment. Cases may over-report ipsilateral use if they believe a cell phone had caused their tumor which may produce a false positive relationship because of recall bias.

DISCUSSION

Most of the literature we reviewed did not associate cell phone use with AN development. These studies generally lacked sufficient statistical power to find excess risks of AN or other brain tumors. However, three separate studies from the Nordic region have reported a significant association between AN development and cell phone use. The Hardell group found a significant linkage between long-term (≥ 10 years) cell phone use and AN. Lönn and Schoemaker groups also found a positive association between long-term ipsilateral cell phone exposure and AN occurrence. These inconsistent results may be explained by differences in study design and in exposure characteristics and assessment, and small sample size of long-term uses. For AN and most brain tumors, a 10-year latency period is believed to be required for development of tumors from any given exposure (12). Longer observation periods and a higher cumulative number of usage hours will need to be observed in order to determine whether there is a relationship between cell phone use and AN or other brain tumors.

In general, several flaws have been discussed among these cell phone studies. The definition of “regular use” in many studies is highly problematic. A “regular cell phone user” in the studies that followed INTERPHONE protocol was someone who made at least a single call per week for six months or more before the diagnosis of AN. Long-term and/or heavy users were not separately evaluated. The approach of combining occasional users with heavy users biases the ability to find any association between AN and cell phone use. In contrast to the INTERPHONE protocol, the Hardell group defined those individuals who started to use a cell phone or cordless phone within one year prior to diagnosis as unexposed. This approach may also underestimate the risk if there is a short latency for AN, because they may have misclassified recent heavy users as unexposed users.

Among the variety of types of cordless and cell phones, only cell phones have elicited concern as a possible cause of brain tumors, especially analogue cell phones. The Hardell group has pooled and analyzed data from two case-control studies and suggested analogue cell phone showed a significantly increased AN risk with a 10-year latency period (OR = 2.2, 95% CI = 1.3-3.8). They found that both digital cell phones and cordless telephones are related to AN development (10). The INTERPHONE studies did not assess the exposure to cordless phones, which also emit radiofrequency. The potential long-term deleterious health effects of long-term cordless phone exposures needs further investigation.

According to the INTERPHONE protocol, when a study subject had died or was too ill to participate, a proxy respondent was interviewed. It is virtually impossible to verify the exposure information provided by surrogates. To eliminate this bias, the Hardell group included only living cases who were judged to be able to answer the questionnaire in order to obtain higher data quality. On the other hand, this approach may miss extreme cases of very heavy use. Observational bias might also be introduced during the interview because variation in administration of a questionnaire might provoke different responses to the same questions.

It should be noted only the Hardell group reported a significant increased AN risk among cell phone users regardless of laterality. Hardell’s found large confidence intervals and did not demonstrate a dose-response relationship, a critical factor to prove causality. It has been suggested that relying on an ipsilateral association as evidence of causation is problematic. However, the latest INTERPHONE study report indicates that AN risk was significantly increased on the side of the head where the phone was held for a 10-years or more (3).

AN remains a tumor with greater biologic plausibility for association with cell phone use, because the acoustic nerve falls directly under the area where the cell phone signal enters the head at the greatest strength. However, changes in diagnostic technique, histological coding/classification of brain tumors, and reporting practices among regions may have caused misclassification to shift. Changes in routine surveillance and use of diagnostic technology may also have led to increased tumor detection with no underlying change in the basic rate. The effect of coding changes based on the International Classification of Disease for Oncology (ICD-O) is unknown. Standardized histopathological verification of cases should be employed in any studies of AN.

Level of exposure to RF energy among cell phone users depends on several factors including the number and duration of calls, the quality of the transmission, how far the antenna is extended, the position of the phone relative to the head and the handset, and especially the age of the user (32). The use of cell phones by children has been increasing exponentially in recent years. The longer lifetime exposure of RF for children who start to use cell phones will result in greater lifetime exposure compared to adults. If adverse effects of RF are more likely to affect developing brains, children could face higher risk of AN or other brain tumors (21). Radiofrequency signals are absorbed deeply into the brains of children.(Figure 1)(8). This exception is important because brains do not fully myelinate and skulls do not mature until the late teen years (4). Yet, none of the present studies included cases younger than age 20.

Except for exposure to high-dose ionizing radiation or from rare inherited genetic syndromes such as Neurofibromatosis Type 2 (20), few risk factors have been identified for AN. Medical ionizing radiation used for diagnosis or treatment including X-ray and CT scans is the major man-made source of radiation. A possible association between diagnostic radiation and meningioma has been reported (22, 27). Environmental exposures including radiofrequency electromagnetic field and frequent exposure to loud or persistent noise are under discussion as a possible risk factors for AN. Occupational exposures to organic solvents, vinyl chloride and other chlorinated hydrocarbons, fuels, lubricating and other oils, pesticides, heavy metals, and N-nitroso-compounds may also be considered potential risk factors for AN, as they are for other brain tumors (6, 17). However, few studies of AN to date have considered these potential causes except for studies from Muscat et al (24) and Schlehofer et al (28) that adjusted for occupations and Schoemaker et al (29) that adjusted for radiotherapy history in their statistical analysis. In other studies, calculations of AN risks and cell phone uses were adjusted to sex, age, and socioeconomic status, but environmental exposures, occupational histories, and medical diagnostic exposures were rarely considered. Without data on these possible risk factors, negative findings may arise from incomplete exposure information resulting in a Type II error.

The absence of long-term prospective studies on cell phone use poses a serious problem for research on this growing modern technology. Case-control studies are limited in their power because of difficulties in characterizing all relevant exposures to RF and failure to address other competing causes. There are no standardized epidemiologic methods or validated questionnaires to measure cell phone use and its association with AN development or other brain tumors. Recently our institution, Center for Environmental Oncology, University of Pittsburgh Cancer Institute, has joined with others in proposing that the cell phone companies provide for independent confidentiality protected, decoded evaluation of their records. Retrieving billing records from networking companies to obtain cumulative cell phone use and collaborating personal interview would provide the capability to validate self-reported cell phone exposure in future studies. Access to such information will allow for the development of long-term studies prospectively that will not be hampered by recall bias regarding type and lengths of cell phones used and would also allow the reconstruction of retrospective analyses of cases and controls. Such access must remain compliant with protected health information of the patient.

Although assessment of cordless phone use cannot be identified from billing records, personal interviews can provide estimates. Conducting follow-up cell phone studies on the usage among children and teenagers, assessing cell phone exposure using industry data, creating standardized questionnaires collecting factors including environmental and occupational exposures, medical radiation, smoking, family history and genes is essential to investigate the possibility of synergism, to adjust potential confounding, and to consolidate current debate on call phone uses and adverse health effects.

CONCLUSION

Nearly 90% of adults use cell phones today, a number that is eight times the rate in 1990. Studies that consider cell phone use in the 1990s cannot indicate the risks, if any, of newer phones that are broadly used today. Because the latency for AN is generally believed to be at least a decade, the ability to find evidence of any risk associated with cell phones is also limited. Recent guidelines have been released advocating precaution in the use of cell phones (2), based on experimental findings and some positive results in human studies (1). Most studies are relied on self-reported history of use of cell phones that cannot easily be validated. Creating independent prospective and retrospective access to cell phone records, along with detailed questionnaires regarding reported patterns of cell phone use and other possible risk factors, is essential in order to evaluate whether or not cell phone use is associated with tumour development.

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Figure legend

Figure 1. Estimation of the absorption of electromagnetic radiation from a cell phone based on age (Frequency GSM 900 Mhz) (On the right, a scale showing the *Specific Absorption Rate* at different depths, in W/kg) (8).

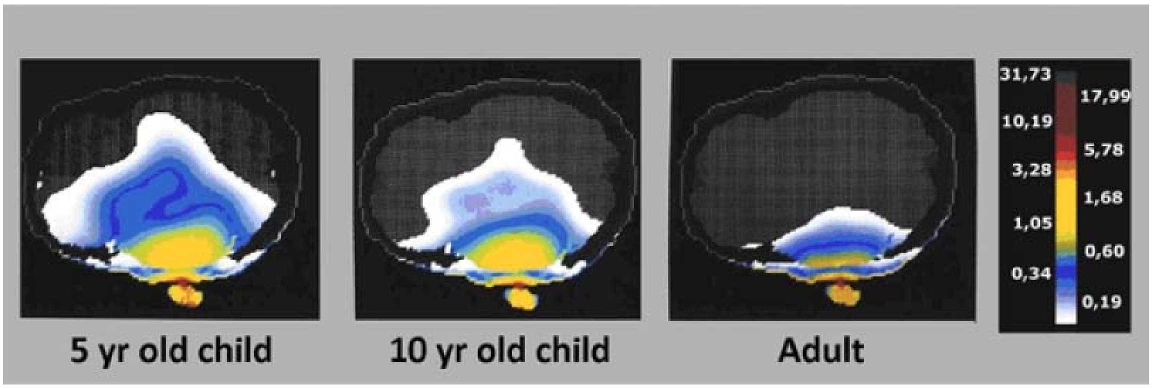
5 yr old child
10 yr old child
Adult
31,73
17,99
10,19
5,78
3,28
1,68
1,05
0,60
0,34
0,19

Table 1. Estimated percentage of cell phone users by country and year

(total cell phone subscriptions/total population)

Year	1994	1998	2002	2005
USA	9.2%	25.2%	48.8%	67.6%
Sweden	15.7%	46.4%	88.9%	93.3%
Norway	13.5%	47.4%	84.4%	102.9%
UK	6.7%	25.1%	84.1%	102.2%
Germany	3.1%	17.0%	72.7%	95.8%
Japan	3.5%	37.4%	63.7%	74.0%
China	0.1%	1.9%	16.1%	29.9%

Table 2. Summary of published articles on acoustic neuroma and cell phone use

Study	Population	Period	Study type	No of cases	No of Controls	OR (95% CI)	Cell phone exposure
Inskip et al., 2001	USA	1994–1998	Case–control	22	172	1.0 (0.5 – 1.9)[1]	Regular use (at least two calls per week)
				5	31	1.9 (0.6 – 5.9)[1]	≥ 5 years of regular use
Muscat et al., 2002	USA	1997–1999	Case–control	7	17	0.5 (0.2 – 1.3)	1-2 years of regular use (having had a subscription to a cell phone service)
				11	6	1.7 (0.5 – 5.1)	3-6 years of regular use
Schüz et al., 2006	Denmark	1982–2002	Cohort	32	43.7	0.7 (0.4 – 1.0)[2]	Regular use [5]
				28	42.5	0.7 (0.4 – 0.95)	≥ 10 years of regular use
Christensen et al., 2004[6]	Denmark	2000–2002	Case–control	45	97	0.9 (0.5 – 1.6)	Regular use [5]
				9	25	0.7 (0.3 – 1.9)	≥ 5 years cumulative use
Lönn et al., 2004[6]	Sweden	1999–2002	Case–control	89	356	1.0 (0.6 – 1.5)	Regular use [5]
				14	29	1.8 (0.8 – 4.3)	≥ 10 years of regular use
Schoemaker et al., 2005[6]	4 Nordic countries, UK	1999–2004	Case–control	360	1934	0.9 (0.7 – 1.1)	Regular use [5]
				47	212	1.1 (0.7 – 1.5)	≥ 10 years of regular use
Hardell et al., 2002	Sweden	1997-2000	Case-Control	38	11	3.5 (1.8 – 6.8)	Regular analogue cell phone use
				26	7	3.7 (1.6 – 8.6)	> 5-year latency of use
Hardell et al., 2005	Sweden	2000-2003	Case-Control	20	79	2.0 (1.1 – 3.8)	Regular digital cell phone use
				11	36	5.1 (1.9 – 14)	>5-10-year latency of digital cell phone use
				53	343	4.2 (1.8 – 10)	Regular analogue cell phone use
				23	111	2.7 (1.3 – 5.7)	>5-10-year latency of analogue cell phone use
Takebayashi et al., 2006[6]	Japan	2000–2004	Case–control	51	192	0.7 (0.4 – 1.2)	Regular use [5]
				4	12	0.8 (0.2 – 2.7)	8+ years cumulative length of use (all brain tumor combined)
Schlehofer et al., 2007[6]	Germany	2000-2003	Case-control	29	74	0.7 (0.4 – 1.2)	Regular use [5]
				8	27	0.5 (0.2 – 1.3)	5-9 years since regular use
Klaeboe et al., 2007[6]	Norway	2001-2002	Case–control	22	227	0.5 (0.2 – 1.0)	Regular use [5]
				8	67	0.5 (0.2 – 1.4)	≥ 6-year latency of cell phone use
Hardell et al., 2008	Sweden		Meta-analysis	824	4261	0.9 (0.7 – 1.1) [3]	Regular use
				83	355	1.3 (0.6 – 2.8) [4]	Using cell phone ≥ 10 years latency period

1. Relative Risk was calculated; 2. Standardized incidence ratio was calculated based on observed and expected numbers; 3. Based on 9 case-control study. 4. Based on 4 case-control study (Lönn et al 2004, Christensen et al. 2004, Schoemaker et al. 2004, and Hardell et al., 2006)
5. Regular cell phone use was defined as having used cell phone at least once a week for more than 6 months
6. Participants of the INTERPHONE study

Table 3. Summary of ipsilateral acoustic neuroma with respect to laterality of regular cell phone use

Study	No of cases	No of Control	OR (95% CI)	Cell phone exposure
Inskip et al., 2001	-	-	0.9 (p=0.6)[1]	Relative risk of AN and ipsilateral cell phone exposure
Muscat et al., 2002	-	-	0.9 (p=0.07)[1]	Relative risk of AN and ipsilateral cell phone exposure
Schüz et al., 2006	N.A.	N.A.		
Christensen et al., 2004	19	57	0.7 (p=0.02)[1]	Relative risk of AN and ipsilateral cell phone exposure
Lönn et al., 2004	48	192	1.1 (0.7 – 1.6)	Regular cell phone use of ipsilateral exposure
	12	15	3.9 (1.6 – 9.5)	≥ 10 years since first regular use of ipsilateral exposure
Schoemaker et al., 2005	187	1061	0.9 (0.7 – 1.1)	Regular cell phone use of ipsilateral exposure
	23	72	1.8 (1.1 – 3.1)	≥ 10 lifetime years cell phone use of ipsilateral exposure
Hardell et al., 2002	93	53	1.8 (1.3 – 2.5)	Ipsilateral exposure of analog phone use and tumor in hemisphere
	30	12	2.5 (1.3 – 4.9)	Ipsilateral exposure of analog phone use and tumor in temporal area
Hardell et al., 2005	12	25	5.1 (1.9 – 14)	Regular analogue cell phone use of ipsilateral exposure
	29	108	2.9 (1.4 – 6.1)	Regular digital cell phone use of ipsilateral exposure
	25	97	2.4 (1.1 – 5.1)	Regular cordless phone use of ipsilateral exposure
Takebayashi et al., 2006	20	73	0.9 (0.5 – 1.6)	Regular mobile phone use of ipsilateral exposure
			0.7 (p=0.01)[1]	Relative risk of AN and ipsilateral cell phone exposure
Schlehofer et al., 2007	N.A.	N.A.		
Klaeboe et al., 2007	11	120	0.7 (0.3 – 1.4)	Regular mobile phone use of ipsilateral exposure
	5	36	0.9 (0.3 – 2.8)	≥ 6 years since first regular mobile use of ipsilateral exposure
Hardell et al., 2008	53	167	2.4 (1.1 – 5.3)[2]	Ipsilateral exposure of cell phone ≥ 10 years latency period

1. Relative Risk was calculated
2. Results from a Meta-analysis, based on three case-control studies (Lönn et al., 2004, Schoemaker et al., 2005 and Hardell et al., 2006)